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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/587,975	GUEDAT ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *15 and 17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/3/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This application is a 371 of PCT/EP05/00388 filed 01/17/2005 and claims priority to French application 04/01046 filed 02/04/2004.

Claims 1-17 are pending.

Response to Restriction/Election

2. Applicant's election of Group I and the species (4-[4-(Ethyl-5- methyl-4-phenyl-lH-imidazol-2-yl)thiazol-2-yl]piperid-l-yl{(6-methyl-4'-trifluoromethoxybiphenyl-2-yl)methanone) in the reply filed on October 8, 2008 is acknowledged. The election was made with traverse, and the examiner finds the arguments unpersuasive. The traversal is on the grounds that the rules 13.1 and 13.2 were complied with, however Rule 13.2 was not complied with and is reproduced below:

13.2 *Circumstances in Which the Requirement of Unity of Invention Is to Be Considered Fulfilled*

Where a group of inventions is claimed in one and the same international application, the requirement of unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

Rue 13.2 states that the "special technical feature" is "those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art." The examiner having clearly shown this "special technical feature" to be lacking, met his burden and properly restricted the application. A further explanation of the lack of a "special technical feature" may be found in the 103(a) rejection below. This application contains claims drawn to a nonelected invention with traverse. Group III is now created to include the new claim 17 drawn to disease treatment. Applicant is advised that should the product claims become

allowable, the method claims shall be rejoined. A complete reply to this action must include a cancellation of nonelected claims or other appropriate action.

Group I, Claims 1-14, 16 drawn to compounds and compositions. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Group II, Claim 15 drawn to methods of preparing compounds. If this group is elected, a further election of a single disclosed species of each of the Formulae I-VII is also required. Further restriction based on the election may be made.

Group III Claim 17 drawn to methods of treating diseases.

Claim Rejections - 35 USC § 112 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 13, recites "other substituents as defined above". It is not clear what above is in reference to.

4. Claims 11 and 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 11, recites "especially" and claim 12 recites "preferably". It is improper to speak of preferred embodiments within a claim. In addition claims 11 and 12 recite "and/or" markush formula should be phrased in the alternative only.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

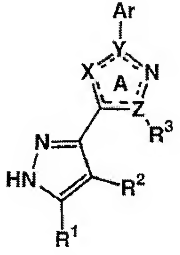
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-2, 6, 7, 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chariffson et. al. WO 2001052845 A1.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

A) Determining the scope and contents of the prior art.
B) Ascertaining the differences between the prior art and the claims at issue.

Chariffson et. al. teach the following genus of compounds:



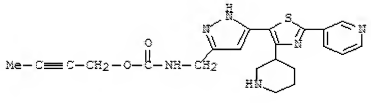
I

Ar is an optionally substituted aryl, heteroaryl, or heterocyclyl ring.

Rings having one to four heteroatoms selected from N, O, or S include heterocyclic aromatic (or heteroaryl) rings and non-aromatic heterocyclic rings. include 2-

2-imidazolyl,

A particular species is the compounds where R3 is 3-piperidiyl, Ar is 3-pyridyl, See compounds (IC-6, ID-6)



At least in the instant claims where R3 of the instant claims is an optionally substituted heteroaryl (pyrazole), G is a bond, R1 is H, the only difference is the selection of the imidazole group as opposed to the other heteroaryls of Chariffson et. al. (pyridine or pyrimidine)

C) Resolving the level of ordinary skill in the pertinent art.

The level of ordinary skill is high. Someone preparing these compounds would be trained in organic and medicinal chemistry and would recognize the very close structural similarity and would expect them to have similar properties. It would be routine for a chemist to prepare analogs differing only in the replacement of a pyridine or pyrimidine with an imidazole.

D) Considering objective evidence present in the application indicating obviousness or nonobviousness.

The compounds of the instant case are analogs of old compounds. One of ordinary skill would be motivated to make the compounds of the invention because he would expect the compounds to have similar properties and increased potency and selectivity. *In re Grabiak* 226 USPQ 870, "[w]hen chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made", *In re Deuel* 34 USPQ2d 1210, "a known compound may suggest its **analogs** or isomers, either geometric isomers (*cis* v. *trans*) or position isomers (emphasis added) (*e.g. ortho v. para*)". Compounds that are active as gyrase inhibitors may be useful for treating bacterial infection. Since Chariffson et. al. suggest that the the Ar ring may be imidazole, without a showing of unexpected results a *prima facie* case of obviousness is appropriate.

Claim Rejections - 35 USC § 112 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-14, 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds it does not reasonably provide enablement for the scope of compounds bearing the extensive list of substituents. The compounds that are enabled are as follows:

R1 and R3 are H

R4 is alkyl, R5 is alkyl

R6 is phenyl or pyridyl

G-R1 is H, Boc, or (C=O)-orthobiphenyl ($S=O_2$)-orthobiphenyl optionally substituted with CF_3, OCF_3, alkyl, CN, OCH3, or halogen

And while being enabled for salts, optical isomers, epimers and tautomers, the claims are not enabled for "amine oxides" or "geometrical isomers".

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing a long list of prophetic groups bearing multiple substitutions **(B) The nature of the invention:** This is a chemical invention requiring the synthesis of compounds and such compounds should have activity at MTP/apoB. **(D) The level of one of ordinary skill**: One of ordinary skill is a practicing organic/medicinal chemist. **(C) The state of the prior art: (E) The level of predictability in the art: (F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:** Each one of the factors **(C, E-H)** will be discussed in light of the scientific literature when such a factor is being directly pointed to a large capital letter referring to the aforementioned Wands factor will be placed directly after such a remark or explication. The examiner will first consider the Markush structure I of claim 1, and discuss the limitations inherent to the chemistry required to prepare the compounds as well as the paucity of available starting materials. The compounds of the instant claims are prepared by the sequence of reactions shown below in Figure 1.

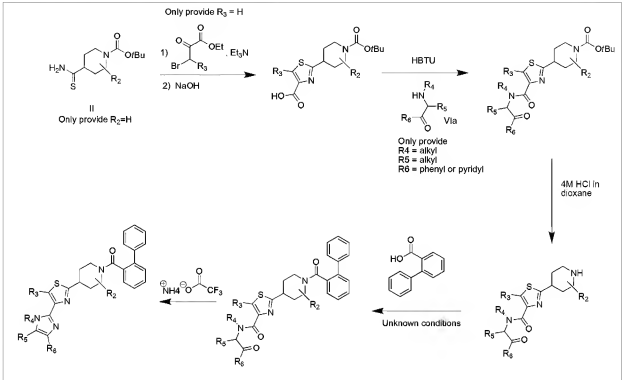


Figure 1. Applicant's synthesis of the instantly claimed compounds.

For the key starting material II, only one compound is provided and it was purchased from Maybridge according to the specification. The examiner conducted a search that reveals only this single compound as available, thus the specification does not provide directions to prepare or buy the diverse array of moieties claimed for R^2. The same can be said for the ethylbromopyruvate which requires a vast array of substituted derivatives to support the instant claims. Both R^2 and R^3 are claimed as

- R^2 and R^3, which may be identical or different, are chosen, independently of each other, from a hydrogen atom, an alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl radical and a radical -NRR';

yet only information provided for in the specification is a compound where both R^2 and R3 are H. Where can one purchase or fine the directions to prepare the compounds needed for the scope of the claims? As per MPEP:

> A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court in In re Ghiron, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. In re Howarth, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

According to the U.S. Court of Customs and Patent Appeals in *In re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 101, "[o]rdinarily no problem in this regard arises since the method of preparing almost all starting materials can be set forth in writing if the materials are not already known and available to the workers in the art, and when this is done the specification is enabling to the public". *In re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 104, "it is essential that there be no question that, *at the time an application for patent is filed,* (emphasis in original) the invention claimed therein is fully capable of being reduced to practice (i.e., that no technological problems, the resolution of which would require more than ordinary skill and reasonable time, remain in order to obtain an operative, useful embodiment)." That is not the situation here. Rather we find no direction as to how the many required staring materials with the vast array of R2 and R3 moieties are to be obtained. **(F)** *In re Howarth*, 210 USPQ 689, (claimed derivatives of clavulanic acid not enabled by specification lacking information of how prepare the clavulanic acid or directions to reference materials containing such information), *Ex parte Schwarze* 151 USPQ 426 (where starting material is not known to art as of date of filing

application, there must be included a description of preparation thereof to enable one skilled in this art to carry out applicant's invention), *Ex parte Moersch* 104 USPQ 122 (claims to process for the production of (1)-y1-p-nitrophenyl-2-dichloracetamindo-propane-1,3-diol not enabled because of failure to describe source or method of obtaining starting compound; although starting compound is identified by means of appropriate name and by structural formula).

The limitations of synthetic chemistry is readily apparent as stated in the preface to a recent treatise:

> ""Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work.....Chemists tend not to publish negative results, because these are, as opposed to positive

> results, never definite (and far too copious) [preface].....even structurally simple compounds often turn out not to be so easy to make as initially thought. [pg. 2]..... As illustrated by the examples discussed below, a good retrosynthesis requires much synthetic experience, a broad knowledge of chemical reactivity, and the ability to rapidly recognize synthetically accessible substructures [pg. 3]..... As will be shown throughout this book, the outcome of organic reactions is highly dependent on all structural features of a given starting material, and unexpected products may readily be formed. [8].....Even the most experienced chemist will not be able to foresee all potential pitfalls of a synthesis, specially so if multifunctional, structurally complex intermediates must be prepared. The close proximity or conformational fixation of functional groups in a large molecule can alter their reactivity to such an extent that even simple chemical transformations can no longer be performed. Small structural variations of polyfunctional substrates might, therefore, bring about an unforeseeable change in reactivity [pg. 9]....." Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface pg. 1-15. **(E)**

The directions for the coupling of the acids i.e. GR1 to the piperidine are not even given:

Step e)

2-[1-(6-Methyl-4'-trifluoromethoxybiphenyl-2-carbonyl)piperid-4-yl]thiazole-4-carbonyl[N-ethyl-N-(1-methyl-2-oxo-2-phenylethyl)]amide

The title compound was obtained according to a procedure similar to that used for the preparation of *tert*-butyl 4-{4-[ethyl(1-methyl-2-oxo-2-phenylethyl)carbamoyl]thiazol-2-yl}piperidine-1-carboxylate.

TLC: 1/1 CH_2Cl_2/EtOAc: Rf = 0.47

LC-MS: (ES+) 650.4 (M+H)

Yield: 68%.

Missing step ?

Step f)

{4-[4-(1-Ethyl-5-methyl-4-phenyl-1*H*-imidazol-2-yl)thiazol-2-yl]piperid-1-yl}(6-methyl-4'-trifluoromethoxybiphenyl-2-yl)methanone

2-[1-(6-Methyl-4'-trifluoromethoxybiphenyl-2-carbonyl)piperid-4-yl]thiazole-4-carbonyl[N-ethyl-N-(1-methyl-2-oxo-2-phenylethyl)]amide (0.195 g; 0.3 mmol) is mixed with ammonium trifluoroacetate (10 eq.; 3.0 mmol; 393 mg) under a nitrogen atmosphere. The mixture is heated for 5 minutes at 150°C with stirring, the heating is removed and water is added.

The reaction medium is then extracted twice with ethyl acetate, and the organic phases are then combined and washed with water, dried over sodium sulfate and then evaporated to dryness to give 0.171 g of a pure white solid, corresponding to the expected product.

TLC: 1:1 CH_2Cl_2/EtOAc; Rf = 0.48

MS: ES+ 632.6

Yield: 90%

These reactions are not trivial as is well known in the MTP inhibitor development art. See Chang et. al. "Microsomal triglyceride transfer protein (MTP) inhibitors: Discovert of clinically active inhibitorsusing high-throughput screening and parallel synthesis paradigms" *Current Opinion in Drug Discovery and Development* **2002**, *5*, 562-570.

With the rather simple structure of compound 1, Pfizer scientists pursued a robotics-assisted parallel synthesis strategy as a means of exploring alternatives for the 4-toluidine moiety, with the goal of improving potency. Unfortunately, the biphenyl carboxylic acid moiety of compound 1 was not suitable for automated organic synthesis. Attempts to activate the acid group for amide formation resulted in exclusive formation of fluorenone 2 (Figure 1). With the intent of deactivating the aromatic ring and, thus, suppressing fluorenone formation, the 4'-trifluoromethyl-2-biphenyl carboxylic acid 3 (Figure 1) was utilized. In this case, amide formation was uneventful and the resulting

The final step which is the synthesis of the imidazole core via the reaction of ammonium acetate with the ketoamide (see Figure 1), is well known to be sensitive to steric effects. See Claibourne et. al. "An Efficient Synthesis of Tetrasubstituted Imidazoles from N-(2-Oxo)-amides" *Tetrahedron Letters* **1998**, *39*, 8939-8942. "Although the method tolerates a versatile array of subtitutents, when R_2 is sterically hindered R_1 appears to be limited to small groups." Both of these references show that even routes that are proposed and closely scrutinized by an expert have a high rate of failure and it is often times difficult or impossible to understand why such chemistry will not work as planned.

Many of the compounds currently under the Markush claim could not exist but would self-polymerize instantaneously if prepared as stated by Dorwald ibid. pg. 41 "It goes without saying that a compound will decompose or oligomerize if it contains functional groups which can react with each other. Because intramolecular reactions often proceed at much higher rates than their intermolecular variants, functional group incompatibilities may arise unexpectedly,

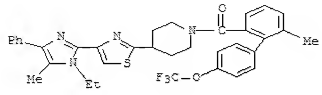
involving groups which would not react intermolecularly…" A notable example is compounds bearing multiple amino groups and alkyliodides. **(C & E)**. The claims are also drawn to "amine oxides" or "geometrical isomers". There are no amines on the instantly claimed compounds that can form N-oxides and no olefins that can give rise to geometrical isomerism and no conditions for the preparation of such compounds.

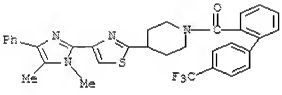
While these chemical limitations are significant, perhaps more significant are the limitations of activity at MTP/apoB. We have not been given any information in regard to the molecular determinants of receptor affinity for the compounds of the instant case for "heteroaryls". In order to clarify, the specification does not exemplify the groups that were under rejection for scope of enablement. In the MTP inhibitor field minor structural variations lead to dramatic changes in activity, See Magnin, D. R. et al. "Microsomal Triglyceride Transfer Protein Inhibitors: Discovery and Synthesis of Alkyl Phosphonates as Potent MTP Inhibitors and Cholesterol Lowering Agents" *Bioorganic & Medicinal Chemistry Letters* **2003**, *13*, 1337–1340.

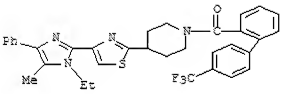
:

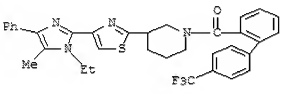
> "as seen in Table 2, modest changes in the amide appendage gave rise to significant changes in activity in the lipid transport assay. For instance, the amide 20 is much more potent than the ester 25. The carboxylate (not shown) was inactive. As a general trend, simple alkyls were more active than alkylaryls (cf. 20 vs 21); however activity could be recovered in the arylalkyl series by additional substitution from the aromatic nucleus (26). Attempts to increase water solubility with either morpholine or pyridyl substituents provided compounds that were markedly less active than 20. The effect of the spacer between the fluorenyl and the phosphonate group was evaluated." Column 1, line 25 to column 2 line 5."

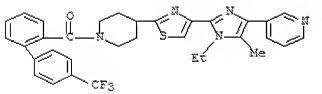
In this case the claimed compounds are relatively homogenous and the rejected groups have no working examples. Only the following seven compounds were actually exemplified:

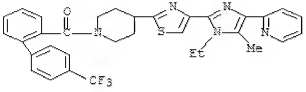


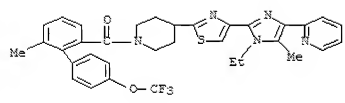










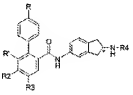


While working examples are not required, in nascent technologies such as the instant case the degree of unpredictability is an important factor. In order to practice the full scope of the invention, one of ordinary skill would not only need to create synthetic procedures *de novo*, but also decide what compounds to prepare. The specification gives literally no guidance with regard to what the requirements for activity are i.e. which substituents would be preferred. It is known in the art that the moiety G-R1 of the instant claims can only be certain things, this group has been described by Chang et. al. as a recurring theme:

> Representative structures from some of these pharmaceutical companies are shown in Figure 3. It is worth noting that the 4'-trifluoromethyl-2-biphenyl carboxylic acid moiety is a re-occurring group in many of these structures.

These compounds must bear a ortho-biphenyl moiety that may be optionally substituted with a very select number of groups, See Ksander et al. "Diaminoindanes as Microsomal Triglyceride

Transfer Protein Inhibitors" *Journal of Medicinal Chemistry*, 2001, 44, 4677-4687, where the ortho-biphenyl moiety substituents were only varied as CF3, CH3, H, CN, OCH3, and halogen, yet several compounds were not active. Table 1 is shown below:



compd	chirality	*R*	R^1	R^2	R^3	R^4	apoB IC_{50} (nM)	MTP IC_{50} (nM)
8aR	R	CF_3	CH_3	H	H	CO_2Me	0.7	70
8aS	S	CF_3	CH_3	H	H	CO_2Me	6.4	70
8bR	R	CF_3	H	H	H	CO_2Me	1.9	68
8bS	S	CF_3	H	H	H	CO_2Me	5.2	110
10bS	S	CF_3	H	H	H	SO_2Ph	1.3	105
10bR	R	CF_3	H	H	H	SO_2Ph	42	650
11aR	R	CF_3	CH_3	H	H	SO_2CH_3	8.8	204
11aS	S	CF_3	CH_3	H	H	SO_2CH_3	1.8	34
11b	racemic	CF_3	H	H	H	SO_2CH_3	60	120
8dR	R	CF_3	H	H	CH_3	CO_2Me	2.2	170
8eR	R	CF_3	CF_3	H	H	CO_2Me	1.8	50
8fR	R	CF_3	H	H	CF_3	CO_2Me	7.5	410
12aS	S	CF_3	CH_3	H	H	SO_2-thienyl	0.9	50
12gS	S	CF_3	CH_3	H	CH_3	SO_2-thienyl	1.0	20
12gR	R	CF_3	CH_3	H	CH_3	SO_2-thienyl	2.6	180
8gS	S	CF_3	CH_3	H	CH_3	CO_2CH_2	2.5	90
8gR	R	CF_3	CH_3	H	CH_3	CO_2CH_2	1.1	70
13b	racemic	CF_3	H	H	H	$COCH_3$	120	80
14b	racemic	CF_3	H	H	H	COPh	270	> 1000
15b	racemic	CF_3	H	H	H	$CON(CH_3)_2$	120	80
16b	racemic	CF_3	H	H	H	CH_2Ph	340	4800
17aR	R	CF_3	CH_3	H	H	CH_2-2-pyr	1.7	100
17aS	S	CF_3	CH_3	H	H	CH_2-2-pyr	36% at 100 nM	410
10h	racemic	F	CH_3	H	H	SO_2Ph	1.2	240
12h	racemic	F	CH_3	H	H	SO_2-thienyl	1.4	50
11h	racemic	F	CH_3	H	H	SO_2CH_3	8.3	170
10i	racemic	CH_3	CH_3	H	H	SO_2Ph	2.5	93
10j	racemic	CN	CH_3	H	H	SO_2Ph	5.5	120
10k	racemic	Cl	CH_3	H	H	SO_2Ph	2.4	100
11k	racemic	Cl	CH_3	H	H	SO_2CH_3	6.6	100
12k	racemic	Cl	CH_3	H	H	SO_2-thienyl	3.0	120
8fR	R	Cl	CH_3	H	CH_3	CO_2Me	3.4	120
10m	racemic	Cl	OCH_3	H	H	SO_2Ph	2	110
11m	racemic	Cl	OCH_3	H	H	SO_2CH_3	15	70
10n	racemic	H	H	H	H	SO_2Ph	12	710

"The trifluoromethyl substituent (R) on the distal aromatic biphenyl ring can be replaced by a fluoro, methyl, cyano, or chloro substituent while maintaining or producing a slight 2-3-fold reduction of inhibitory activity. In the absence of a para substituent (R) H) a 10-fold reduction of apoB inhibitory activity was observed. It was found that the 2-aminoindane nitrogen could be incorporated in a piperazine ring (Table 2) and maintain good in vitro activity.".

It is clear that a skilled worker or rather a small army (25) of skilled workers can experiment to some degree in terms of substituents, however these are the relatively small changes of as CF_3, CH_3, H, CN, OCH3, and halogen. See also Peukert et. al. "Identification and structure–activity relationships of ortho-biphenyl carboxamides as potent Smoothened antagonists inhibiting the Hedgehog signaling pathway" *Bioorganic & Medicinal Chemistry Letters* **2009**, *19*, 328–331.

"We next explored the influence of the biphenyl substituents R1, R2, and R3 on Hh potency. Moving the methyl group from the ortho to the para position on the lower phenyl ring (compounds 7 and 9) resulted in a drastic decrease of activity. Other substituents such as the methoxy group in compound 10 in the R3-position were not tolerated either. Replacing the ortho methyl substituent with a hydrogen yielded compound 11 with a slight drop in activity compared to the corresponding analogue 7. Finally, substituents R1 play a crucial role for activity, too: The trifluoromethyl substituent is the best substituent identified so far; both chloro and hydrogen in this position (compounds 12 and 13) resulted in lower activity.....Replacing the phenyl substituent (6b) with either a 2-pyridyl or 4-pyridyl substituent (7b, 14b) resulted in a □5- to 7-fold drop in potency in the Hh assay and a stronger drop in binding affinity to the mouse Smo receptor. Substitutions on the phenyl ring were not well tolerated and the activity of compounds 15b and 16b with para-substituents on the phenyl group dropped significantly. The same was true by replacing the pyridyl group with a bicyclic aromatic group such as the 3-quinolinyl moiety in compound 19b. Substitution on the methylene unit, including the methyl and trifluoromethyl substituents in compounds 17b and 18b were well tolerated and resulted in only slightly less potent Hh inhibitors compared to compound 6b."

According to the specification these rings can contain the following definitions and substitutions, bearing the long list below:

The term "aryl" denotes a monocyclic, bicyclic or tricyclic aryl radical containing from 6 to 14 carbon atoms, optionally substituted by one or more chemical species, which may be identical or different, chosen from a halogen atom, a hydroxyl, thiol, -NRR' (in which R and R', which may be identical or different, are as defined above), cyano, nitro or carboxyl group, and an alkyl, especially substituted by one or more halogen atoms, in particular perhaloalkyl, for instance trifluoromethyl, alkenyl, alkynyl, alkoxy, alkenyloxy, alkynyloxy, alkylthio, alkyldisulfanyl (alkyl-S-S-), alkylsulfinyl (alkyl-S(=O)-), alkylsulfonyl (alkyl-$S(=O)_2$-), alkenylthio, alkynylthio, a phosphoric acid derivative [$(alkyl\text{-}O)_2$-P-O-alkyl], alkylcarbonyl, alkoxycarbonyl, alkylcarbonylamino, alkoxycarbonylamino, arylcarbonyl, arylcarbonylamino, (di)alkylaminocarbonyl, cycloalkyl, cycloalkoxy, cycloalkylthio, heterocycloalkyl, heterocycloalkoxy, heterocycloalkylthio, aryl, aryloxy, arylthio, heteroaryl, heteroarylcarbonyl, heteroaryloxy or heteroarylthio radical.

Aryl radicals that may be mentioned, in a non-limiting manner, include phenyl, naphthyl, anthryl and phenanthryl radicals.

The term "heteroaryl" denotes a monocyclic, bicyclic or tricyclic aromatic radical containing a total of from 3 to 13 atoms, among which 1, 2, 3 or 4 are chosen, independently of each other, from nitrogen, oxygen and sulfur, optionally in oxidized form (in the case of nitrogen and sulfur), the other atoms being carbon atoms, the said heteroaryl radical being optionally substituted by one or more chemical species, which may be identical or different, chosen from a halogen atom, a hydroxyl, thiol, -NRR' (in which R and R', which may be identical or different, are as defined above), cyano, nitro or carboxyl group, and an alkyl, especially substituted by one or more halogen atoms, in particular perhaloalkyl, for instance trifluoromethyl, alkenyl, alkynyl, alkoxy, alkenyloxy, alkynyloxy, alkylthio, alkyldisulfanyl (alkyl-S-S-), alkylsulfinyl (alkyl-S(=O)-), alkylsulfonyl (alkyl-S(=O)$_2$-), alkenylthio, alkynylthio, alkylcarbonyl, alkoxycarbonyl, alkylcarbonylamino, alkoxycarbonylamino, arylcarbonyl, arylcarbonylamino, (di)alkylaminocarbonyl, cycloalkyl, cycloalkoxy, cycloalkylthio, heterocycloalkyl, heterocycloalkoxy, heterocycloalkylthio, aryl, aryloxy, arylthio, heteroaryl, heteroarylcarbonyl, heteroaryloxy or heteroarylthio radical.

It is the conclusion of the examiner as shown by the state of the art both in chemistry and the MTP drug development art that the full scope of the claims is not enabled. The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention that has no working examples in this unpredictable art without undue experimentation.

7. Claims 1-14, 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making hydrates (which are solvates), of the claimed compounds. The specification does not enable any person skilled in the art of synthetic organic chemistry to make the invention commensurate in scope with these claims. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. In the present case the important factors leading to a conclusion of undue experimentation are the absence of any working example of a formed solvate, the lack of predictability in the art, and the broad scope of the claims.

a) Determining if any particular substrate would form a solvate or hydrate would require synthesis of the substrate and subjecting it to recrystallization with a variety of solvents, temperatures, pressures, and humidity. The experimentation is potentially open-ended. b) The direction concerning the hydrates is not found in the specification. c) There is no working example of any hydrate or solvate formed. The claims are drawn to solvates, yet the numerous examples presented all failed to produce a solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed

compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

d) The nature of the invention is chemical synthesis, which involves chemical reactions. e) g) Chemical reactions are well-known to be unpredictable, *In re Marzocchi*, 169 USPQ 367, *In re Fisher*, 166 USPQ 18. The state of the solvate art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). West, Anthony R., "Solid State Chemistry and its Applications, Wiley, New York, 1988, pages 358 & 365. The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is their compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometery of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. In the same paragraph on page 365 West (Solid State Chemistry) explains that it is possible to make meta-stable non-equilibrium solvates, further clouding what Applicants mean by the word solvate. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent

or even the moisture of the air that might change the stabile region of the solvate. h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula I as well as the presently unknown list of solvents embraced by the term "solvate". Thus, the scope is broad.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

Conclusion

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571)272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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D.K.O.

/Rita J. Desai/
Primary Examiner, Art Unit 1625